REMARKS/ARGUMENTS

With this amendment, claims 1, 3-14, 25-35, and 70-71 are pending. Claims 2, 15-24 and 36-69 are cancelled without prejudice. For convenience, the Examiner's rejections are addressed in the order presented in a June 11, 2008, Office Action.

I. Status of the claims

Claims 1 and 25 are amended to recite that colorectal mucosal tissue is the only site of initial contact between the immunogenic peptide and the subject. Support for this amendment is found throughout the specification, for example, at page 33, lines 33-35; page 34, lines 13-15 and lines 29-33; page 35, lines 20-23; page 36, lines 1-9 and lines 33-35; page 37, lines 11-14 and lines 23-25; page 38, lines 3-9; page 39, lines 21-27. Claims 6 and 27 are amended to recite that the purified cytokine is contacted to a colorectal mucosal surface. Support for this amendment is found throughout the specification, for example, at page 36, lines 1-9. As indicated in a declaration from Dr. Jay Berzofsky, colorectal is a standard term in the field, used to refer to the colon and rectum. Support for colorectal administration is found throughout the specification, for example, at page 5, line 37 through page 6, line 1 and at page 21, lines 17-21. These amendments add no new matter.

New claim 70 depends from claims 1 and 25 and recites administration of an interleukin-12 (IL-12) protein to the subject. New claim 70 depends from claim 71 and recites contacting the IL-12 protein with a colorectal mucosal surface. Support for this amendment is found throughout the specification, for example, at page 36, lines 1-9 and at Example 11, page 45 and Figure 15.. These amendments add no new matter.

II. Rejections under 35 U.S.C. §103(a)

The claims 53, 55, 58-61, and 63 are rejected as allegedly obvious over various combinations of references. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. Recently, in reviewing this standard, the Supreme Court noted that any analysis supporting a rejection under § 103(a) must be made explicit, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed." *KSR Intl Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

While the Court warned against a "rigid application" of the TSM test, the Court also found that these questions could provide a "helpful insight" in determining whether the claimed subject matter is obvious under § 103(a). *Id.* at 1396-1397. *See also*, Memorandum to Technology Directors from Margaret A. Focarino, Deputy Commissioner for Patent Operations, May 3, 2007.

A. Klavinskis et al., and Ahlers et al. or Berzofsky et al.

Claims 1, 3, 4, and 25 are rejected as allegedly obvious over Klavinskis *et al. J. Immunol.* 157:2521-2527 (1996) and either Ahlers *et al. J. Immunol.* 158:3947-3958 (1997) or Berzofsky *et al.* WO 94/26785. According to the Office Action, Klaviskis *et al.*, discloses rectal and vaginal immunization using an SIV antigen linked to a cholera toxin. This immunization allegedly resulted in production of antigen-specific cytotoxic T lymphocytes (CTLs). Ahlers *et al.* and Berzofsky *et al.* allegedly disclose the recited antigenic sequence, SEQ ID NO:9. According to the Office Action, one of skill would have been motivated to practice the claimed invention by a suggestion of Klavinskis *et al.* that to prevent dissemination of HIV to the regional lymph nodes, an effective vaccine may need to stimulate CTLs in the rectal or genital tract. Office Action at page 3.

Applicants respectfully disagree. The claimed method is immunization of a subject by administering SEQ ID NO:9 using only colorectal tissue as the site of administration of the vaccine. In contrast, Klavinskis *et al.* disclose only a combination immunization schedule. That is, Klavinskis *et al.* teach administration at a rectal or vaginal site, followed by three oral administrations of the vaccine. Klavinskis *et al.* provide no suggestion or motivation to reduce or eliminate the oral administration for the vaccine.

Applicants submit as Exhibit A, a declaration from inventor, Dr. Jay Berzofsky. Dr. Berzofsky first states that the claimed peptide (SEQ ID NO:9) and the peptide exemplified in the specification (Seq ID NO:2) share the identical immunogenic helper peptide sequence and slightly different variations of the same immunogenic CTL epitope sequence. Thus, Dr. Berzofsky believes that similar immune responses would be generated by both peptides.

Dr. Berzofsky states that on reading Klavinskis *et al.*, in his opinion, a skilled artisan would understand that the three additional oral administrations of antigen were **required** to raise an immune response against the antigen. Thus, Klavinskis *et al.* teach away from the claimed invention, which requires administration of antigen only to a colorectal site. The other cited references, Ahlers *et al.* and Berzofsky *et al.*, do not disclose colorectal administration of an HIV antigen. Therefore, the claimed invention is not obvious in view of the cited references.

B. Klavinskis et al., and Ahlers et al. or Berzofsky et al., in further view of Kiyono et al.

Claims 1, 5-14, and 25-35 are rejected as allegedly obvious over Klavinskis *et al.* and either Ahlers *et al.* or Berzofsky *et al.*, in further view of Kiyono *et al.* Advanced Drug Delivery Reviews 18:23-51 (1995). According to the Office Action, Ahlers *et al.* teach administration of a cytokine with a peptide of SEQ ID NO:9 and Kiyono *et al.* provide motivation to do so by allegedly suggesting that Th cell-derived cytokines are essential for the induction of appropriate antigen-specific mucosal immune responses. Office Action at page 5.

Ahlers *et al.* and Kiyono *et al.* disclose only subcutaneous administration of cytokine with antigen. *See, e.g.*, Ahlers *et al.* at page 3948, top right column and Kiyono *et al.*, pages 41-42. Claims 6, 27, and 71, recite administration of a cytokine to a colorectal mucosal

surface. The specification demonstrates that colorectal administration of IL-12 with SEQ ID NO:2 provides a significant increase in CTL level in both mucosal and systemic sites as compared to colorectal administration of SEQ ID NO:2 without IL-12. *See, e.g.*, specification at page 36, lines 1-9. In addition, intraperitoneal (IP) treatment with IL-12 combined with the colorectal immunization of SEQ ID NO:2 did not increase CTL levels. *See, e.g.*, specification at Example 11, page 45 and Figure 15. As above, according to Dr. Berzofsky, similar immune response are raised by SEQ ID NO:2 and the claimed SEQ ID NO:9.

In his declaration, Dr. Berzofsky states that the activity of cytokine after administration to a colorectal mucosal surface was surprising. Unlike subcutaneous administration, colorectal administration requires the cytokine to retain activity after passing through the hostile environment of the colon. To maintain activity, a cytokine protein must maintain a specific, active structure to allow binding to a cytokine receptor on an appropriate cell. An active cytokine protein requires some minimum of the amino acid sequence to be present in a tertiary structure that is recognized by an appropriate cytokine receptor. According to Dr. Berzofsky, the colon is colonized by bacteria and contains bacterial proteases that can degrade the amino acid sequence of proteins, including cytokines. Thus, according to Dr. Berzofsky, one of skill would not expect the administered cytokine to be active after administration to the colon. In addition, Dr. Berzofsky states that, in order to reach cells that express a cytokine receptor, the cytokine had to pass from the colorectal space and through a protective layer of mucus. The passage of the cytokine through the mucus layer and maintenance of activity would not have been expected by those of skill in Dr. Berzofsky's opinion. Therefore, at a minimum, claims 6, 27, and 71, which recite administration of a cytokine to a colorectal mucosal surface in combination with colorectal administration of SEQ ID NO:9, are not obvious in view of the cited references.

In view of the above amendments and remarks, withdrawal of the rejection for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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EXHIBIT A